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changes can be seen on the relevant pages.

Rejection of claims 1-13 under 35 U.S.C. § 112, first paragraph

Claims 1-13 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to meet the written description requirement.

The Examiner states, "[a]s presently worded, the claims have sufficient breadth of scope to encompass arrays of oligonucleotides that can be of virtually any length, up to 599 nucleotides in length... The aspect of one of skill in the art being able to effectively produce pure populations of oligonucleotides of lengths up to 599 nucleotides in length is critical to enabling the making and use of the claimed invention." The Examiner states further that Jones (U.S. Patent 5,858,671) discloses that the inherent obstacle in synthesizing oligonucleotide arrays is inefficient oligonucleotide synthesis.

Applicant submits that claim 1 and dependent claims 3-13 claim "an array comprising a plurality of **nucleic acid members**, each member having a unique position and stably associated with a solid substrate, wherein each nucleic acid member comprises a non-coding sequence present in a 3'-end of an RNA transcript, and wherein each of said nucleic acid members is less than 600 nucleotides.

Applicant also submits that claim 2 and dependent claim 3, 7, 8, and 10-13 claim "an array comprising a plurality of **nucleic acid members**, each member having a unique position and stably associated with a solid substrate, wherein each nucleic acid member comprises a non-coding sequence present in a 5' end of an RNA transcript, and wherein each of said nucleic acid members is less than 1000 nucleotides.

Claims 1-13 are not limited to an array comprising a "pure population of oligonucleotides", as stated by the Examiner. Therefore, in order to satisfy 35 U.S.C. § 112, first paragraph, the specification need not teach how to prepare each oligonucleotide up to 599 nucleotides in length.

A "nucleic acid member" is defined in the specification at p. 10, lines 28-30, as "either a single stranded or double stranded nucleic acid which comprises a noncoding sequence present at

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either the 3'-end or the 5'-end of an mRNA transcript." Clearly, a "nucleic acid member" would encompass, but is not limited to an oligonucleotide.

The specification also discloses methods for preparing a plurality of nucleic acid members that would be accepted by one of skill in the art as suitable for preparing a nucleic acid member up to 599 nucleotides in length.

It is stated in the specification at p. 18, line 17-p.19, line 11,

"the invention provides a method of producing a cDNA array comprising noncoding sequences present at the 3'-ends of RNA transcripts. The method comprises selecting a cDNA sequence at random from a population of cDNA sequences (e.g., from a cDNA clone library, or a population of reverse transcription products, or RNA amplification products)...The sequence of at least a portion of the 3'-end of the cDNA is determined to identify a complementary sequence suitable for use as an amplification primer (e.g., a 3'-end PCR primer).

Amplification is performed by contacting a cDNA with the appropriate 3'-end primer, a polymerase, nucleotides, and an amplification buffer. The 3'-end primer is extended by the polymerase to generate a nucleic acid member which comprises the noncoding sequence present at the 3'-end of an RNA transcript corresponding to the cDNA. In one embodiment of the invention, the cDNA comprises at least one constant sequence (e.g., vector sequences or an adapter sequence) contiguous with a sequence at the 5'-end of the cDNA molecule and present in each cDNA in the population. A primer corresponding to the constant sequence end of the molecule is included in the amplification reaction to generate an amplified sequence which comprises the non-coding sequence present at the 3'-end of an RNA transcript corresponding to the cDNA and at least a portion of the constant sequence. Amplification methods are known in the art and include, but are not limited to, PCR using single or multiple primers, self sustained sequence replication (Guatelli et al., Proc. Natl. Acad. Sci. USA 87: 1874-1878, 1990), transcriptional amplification (Kwoh, et al., Proc. Natl. Acad. Sci. USA 86: 1173-1177, 1988), Q-Beta Replicase (Lizardi et al., Bio/Technology 6: 1197, 1988), ligase chain reaction (LCR) (see Wu and Wallace, Genomics 4: 560, 1989, Landegren et al., Science 241: 1077 (1988)), nucleic acid based sequence amplification (NASBA), and the like."

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A similar method for producing the nucleic acid members of a cDNA array comprising nucleic acid members wherein the non-coding sequence is present at the 5'-end of an RNA transcript is described in the specification at p. 19, line 27- p. 20, line 11.

The specification also states in Example 2 at p. 41, line 23- p. 42, line 15,

"Microarrays of 5'-end cDNA sequences are constructed using techniques routinely used in the art (e.g., 5' RACE, random priming or oligo dT priming and size selection of RNAs, CapFinder PCR cDNA Library Construction) or using commercially available libraries (e.g., CLONTECH's 5'-STRETCH PLUS cDNA Libraries). cDNAs containing 5'-end noncoding sequences can also be obtained by size selecting for longer clones (according to methods well known in the art), and sequencing the resulting clones. Alternatively, cDNAs containing 5'-end noncoding sequences, but lacking sequence that is not a "sequence at the 5' end", as defined hereinabove, are obtained by using two gene-specific primers for cDNA isolation.

In one embodiment, a human cDNA microarray is produced from clones selected at random from a clone collection enriched in 5'-non-coding sequences, as diagrammed in Figure 1B. Plasmid DNA of each clone is isolated and characterized as described above in Example 1. The purity of the plasmid is further determined by sequencing approximately 300-600 base pairs of the 5' end of the cDNA insert with a vector-specific primer.

Based on the 5' sequence information, an insert-specific primer (e.g., complementary to at least a portion of the 5'-end) is selected (either synthesized or obtained commercially) after identifying (either visually or using a computer program, such as BLAST) a 5'-end primer sequence (insert-specific primer) which will specifically amplify approximately 350 bases of the 5' end of the cDNA. In one embodiment of the invention, PCR is performed using two primers, the 5'-end primer sequence and a vector specific primer complementary to a vector sequence on the strand of the vector which is opposite to the strand from which the 5'-end primer sequence is obtained. After PCR with the insert-specific and vector-specific primers, the presence of a single PCR product of the correct length is confirmed by gel electrophoresis."

In view of all of the above, Applicant submits that claims 1-13 are fully supported by the specification in that the specification clearly and in detail describes how to make an array comprising a plurality of nucleic acid members, as claimed in claims 1 and 2 and dependent claims 3-13. It is also submitted that there is no requirement in the language of claims 1-13

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which would render the specification inadequate under § 112 if it describes how to produce a nucleic acid member less than 600 nucleotides in length but does not describe oligonucleotide synthesis, how to produce an oligonucleotide of less than 600 nucleotides in length or how to address the difficulties in producing an oligonucleotide of that length. Claims 1-13 claim a nucleic acid array comprising "a plurality of nucleic acid members". The instant application clearly teaches art-accepted methods for producing a nucleic acid member that is less than 600 nucleotides in length.

In view of all of the above, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112, first paragraph rejections of claims 1-13.

Rejection of claims 1-13 under 35 U.S.C. § 112, first paragraph

Claims 1-13 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to meet the written description requirement.

The Examiner states, [a]s presently worded, the claimed array can be comprised of nucleic acid sequences that are less than 600 bases in length and which are not present in any public database (claims 1 and 8). In view of an independent claim encompassing all of the limitations of any of its dependent claims, claims 1-13 have been interpreted as encompassing non-known/not publicly available sequences."

Claim 1 and dependent claims 3-7 and 9-13 claim "an array comprising a plurality of **nucleic acid members**, each member having a unique position and stably associated with a solid substrate, wherein each nucleic acid member comprises a non-coding sequence present in a 3'-end of an RNA transcript, and wherein each of said nucleic acid members is less than 600 nucleotides."

Claim 2 and dependent claims 3, 7, and 10-13 claim "an array comprising a plurality of **nucleic acid members**, each member having a unique position and stably associated with a solid substrate, wherein each nucleic acid member comprises a non-coding sequence present in a 5' end of an RNA transcript, and wherein each of said nucleic acid members is less than 1000 nucleotides."

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Claims 1-7 and 9-13 therefore are not limited to non-known/not publicly available sequences, although they could encompass such sequences.

Claim 8 claims "the array of claim 1 or 2, wherein at least 2% of the nucleic acid members on the array comprise sequences which are not included within a public database."

The claimed arrays of claims 1-13 are useful for a variety of applications including: analyzing the expression of a gene or group of genes, comparing the expression profile of a gene in a biological system derived from a healthy versus a diseased individual, determining the biological relevance of a previously unknown or uncharacterized gene, identifying interactions between known or unknown genes, determining the effects of a drug or set of drugs on gene expression and identification of novel genes.

The Examiner states that the specification does not provide a description of the non-known sequences.

The written description requirement under 35 U.S.C. § 112, first paragraph requires that the disclosure of the application relied upon reasonably conveys to the skilled artisan that the inventor had possession of the claimed subject matter as of the filing date of the application.

Claim 8 refers to nucleic acid members whose sequences are not publicly known. Applicant submits that there is no legal requirement, nor is it possible, to describe such unknown sequences of these nucleic acid members.

Applicant submits that nucleic acid members and their methods of production are described clearly and in detail in the specification, as discussed in Applicant's response to the 35 U.S.C. § 112, first paragraph rejection of claims 1-13.

Applicant submits that an "unknown sequence" is described in the specification at p. 12, lines 1-12 as "a sequence not included in a public nucleic acid sequence database at the time the array was generated, either as a complete gene sequence, a partial gene sequence, a cDNA, or an expressed sequence tag (EST)."

Further, the specification teaches how to identify an unknown sequence. It is stated in the specification at p. 4, lines 20-25, "[i]n a further embodiment of the invention, the sequence information obtained from at least a portion of the 3'-end of the cDNA is compared to sequence

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information in a public database, and the cDNA is identified as a known sequence if there is substantial identity between the sequence of at least a portion of the 3'-end and a sequence in the database. If there is no substantial identity, the cDNA is identified as an unknown sequence, and sequence information relating to the cDNA is stored within the memory of a computer or a computer program product."

The specification clearly defines "substantial identity", as it refers to a sequence, at p. 21, lines 5-16 as follows.

"The term 'substantial sequence identity' in the context of two or more nucleic acid sequences refers to one or more sequences or subsequences that have at least 95% percent identity over a comparison window consisting of a specified number of nucleotides after having been compared and aligned for maximum correspondence using a sequence comparison algorithm, or, alternatively by manual alignment and visual inspection. In one embodiment, a sequence having substantial sequence identity is a sequence which has at least 95% nucleotide sequence identity to a sequence in the database (a reference sequence) when aligned for maximum correspondence over a comparison window of 100 contiguous nucleotides, and preferably, 50-600 nucleotides. In a further embodiment of the invention, the sequence has at least 97% identity to the reference sequence when aligned for maximum correspondence over 200 nucleotides. Preferably, the sequence has 100% identity to the reference sequence when aligned for maximum correspondence over 200 nucleotides."

The specification teaches six methods of aligning sequences for comparison at p. 21, lines 18-28. The specification also teaches search tools for performing sequence alignments at p. 22, as well as a clustering algorithm for classifying sequences as known or unknown, at p. 23. Figure 2 of the instant application presents a diagram of a method for classifying sequences as known or unknown.

Applicant submits that as of the filing date of the instant application, Applicant was clearly in possession of the claimed invention, and have put the public in possession of the claimed invention. That is, applicant has clearly described "an array comprising a plurality of nucleic acid members, each member having a unique position and stably associated with a solid

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substrate, wherein each nucleic acid member comprises a non-coding sequence present in a 3'-end of an RNA transcript, and wherein each of said nucleic acid members is less than 600 nucleotides, as claimed in claim 1 and dependent claims 3-7 and 9-13. Applicant has also clearly described "an array comprising a plurality of nucleic acid members, each member having a unique position and stably associated with a solid substrate, wherein each nucleic acid member comprises a non-coding sequence present in a 5' end of an RNA transcript, and wherein each of said nucleic acid members is less than 1000 nucleotides", as claimed in claim 2 and dependent claims 3, 7 and 10-13. Applicant has also described how to identify a nucleic acid member comprising an unknown sequence and thus have adequately described the array of claim 8 wherein "at least 2% of the nucleic acid members on the array comprise sequences which are not included in a public database." Thus, in view of all of the above, Applicant was clearly in possession of the claimed invention of the instant application as of the filing date and have fulfilled the requirements of 35 U.S.C. § 112, first paragraph.

In view of the above, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112, first paragraph rejection of claims 1-13.

Rejection of claim 4 under 35 U.S.C. § 112, second paragraph

Claim 4 is rejected under 35 U.S.C. § 112, second paragraph for alleged indefiniteness. The Examiner states that "claim 4 is indefinite for the recitation of "substantially noncoding sequences".

Claim 4 has been amended to claim "the array of claim 1 or 2, wherein each said nucleic acid member comprises primarily noncoding sequences."

Support for this amendment is presented in the specification at p. 9, lines 20-23 wherein it is stated, "[p]referably, the "3'-end of an mRNA" includes primarily noncoding sequences (90%-100% of the 3' end is untranslated or noncoding sequence), and thus includes only a relatively short portion that is translated, or is part of a coding region." Additional support for this amended is presented in the specification at p. 9, line 30- p.10, line 2, wherein it is stated, "[p]referably, the "5'-end of an RNA transcript" includes primarily noncoding sequences (90%-

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100% of the 5' end is untranslated or noncoding sequence), and thus includes only a relatively short portion that is translated, or is part of a coding region."

Thus, the phrase "primarily noncoding sequences" is defined in the specification as 90-100% noncoding sequences.


Applicant submits that the metes and bounds of the phrase "substantially noncoding sequences" which is now amended to "primarily noncoding sequences" are clearly disclosed in the instant application.

In view of the above, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112, second paragraph rejection of claim 4.

Applicant submits that, in view of the above, the claims are patentable and are in condition for allowance. A notice of allowance to that effect is respectfully requested.

Respectfully submitted,

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Marked-up sheet for claim amendment

4. (Amended) The array of claim 1 or 2, wherein each said nucleic acid member comprises
[substantially] primarily noncoding sequences.